- a product of a Maillard reaction;
- a polymer;
- a chitosan and a chitosan derivative; and
- combinations thereof.

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REMARKS

I. Claim amendment

The Office Action Summary provides that claims 1-36, 40-42, 45 and 46 are pending. The Examiner's attention is directed to claim 47 which was added by the Preliminary Amendment, filed October 5, 2001.

Claim 1 has been amended to recite that the claimed invention is directed to an oral pharmaceutical formulation. Furthermore, when the additive is a lipid, claim 1 has been amended to clarify that medium chain glycerides or a mixture of medium chain glycerides are excluded. Support for the amendment is provided by the specification as originally filed, e.g., page 4, line 8, and page 6, lines 12-13. Therefore, the claim amendment does not introduce new matter.

Claims 22, 35 and 36 have been cancelled in view of amended claim 1. All of the remaining pending claims are either directly or indirectly dependent upon amended claim 1.

II. Claim rejection - obviousness-type double patenting

Claims 1, 30-35, 45 and 46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-10, 24, 25 of US 6,372,728 (the "'728 patent"). On page 3 of the Office Action, the Examiner states that the additives of the rejected claims overlap with the additive used in the '728 patent.

The additive of the '728 patent is a medium chain glyceride or a mixture of medium chain glycerides. Claim 1 has been amended to clarify that medium chain glycerides or a mixture of medium chain glycerides are expressly excluded when the additive agent is a lipid. Thus, there is no overlap between the claims of the '728 patent and the amended claims of the subject application. Accordingly, withdrawal of the rejection is requested.

III. Claim rejection – 35 U.S.C. §102

Claims 1-4, 6, 7, 12-14, 29-42, 45 and 46 are rejected under 35 U.S.C. §102(b) for lack of novelty in view of WO 88/00829 ("WO '829"). The Examiner alleges that WO '829 teaches the use of the claimed bisphosphonate in combination with the claimed additives for the treatment of osteoporosis.

Anticipation requires that each and every element of the claimed invention be disclosed within a single prior art reference. As amended, the claimed invention is directed to an ***oral*** pharmaceutical formulation comprising a bisphosphonate and the recited additives. In contrast, WO '829 discloses a pharmaceutical formulation for ***nasal*** administration comprising a bisphosphonate and certain enhancers.

As such, WO '829 does not disclose each and every feature of the claimed invention and fails, therefore, as an anticipatory reference. Withdrawal of the §102 rejection is requested.

IV. Claim rejection – 35 U.S.C. §103

Claims 5, 8-11, 15-28 and 47 are rejected under 35 U.S.C. §103 as being obvious over WO '829 and US 5,759,586 to Fuchs et al. (the "'586 patent").

A. WO 88/00829

As amended, the claimed invention is directed to an oral pharmaceutical formulation whereas WO '829 is directed to a nasal dosage form. It is well known in the pharmaceutical industry that there are different considerations and requirements for preparing different types of dosage forms, e.g., oral and nasal dosage forms. The different requirements have a direct effect on the stability and pharmacological behavior of the active ingredient. In view of the fact that WO '829 is directed to a nasal dosage form, WO '829 does not provide an enabling disclosure for preparing an oral formulation.

Moreover, WO '829 provides that oral absorption is poor and accompanied by gastrointestinal side effects. Although WO '829 discloses penetration enhancers to be used with nasal dosage forms, WO '829 does not disclose which additives may be added to an oral formulation comprising a bisphosphonate to improve absorption and reduce gastrointestinal side effects.

In summary, therefore, WO '829 does not provide an enabling disclosure for preparing an oral formulation. Although WO '829 discloses that enhancers may be used to improve the nasal administration of bisphosphonates, there is no disclosure or suggestion that a bisphosphonate can be formulated with the additives of claims 5, 8-11, 15-28 and 47 to form the claimed oral pharmaceutical formulation. For all of the foregoing reasons, withdrawal of the §103 rejection based on WO '829 is requested.

B. US 5,759,586

As background, the '586 patent discusses various methodologies for the treatment of osteoporosis. These therapies include the administration of estrogens, calcitonin and bisphosphonate derivatives (col. 2, lines 58-60). However, the therapy of the '586 patent is based on an alternative approach regarding the formation of osteoporosis, i.e., by regarding the formation of osteoporosis from the point of view of the acid-base balance (col. 4, lines 1-6).

Thus, the '586 patent is completely silent on the possibility of using bisphosphonates in the treatment of osteoporosis. Rather as disclosed in claim 1 and column 3, lines 57-67, the composition of the '586 patent comprises the following:

1. sodium, potassium, magnesium and calcium ions
2. at least sodium and potassium are present as carbonates and/or bicarbonates, and
3. enzyme activators.

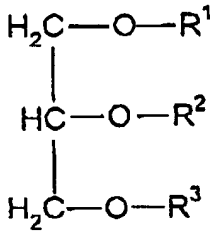
According to the '586 patent, the decisive feature of the composition is that the above-mentioned electrolytes (1) are bound to alkaline or alkalizing agents (2) (col. 5, lines 35-38). One of the preferred anions is glycerophosphate (col. 5, line 63). Examples of the enzyme activators (3) include Li ions and vitamins (col. 5, lines 55-60).

It is evident, therefore, that the composition of the '586 patent does not include any bisphosphonate. In fact, the '586 patent teaches away from the use of bisphosphonates in the sense that it provides an alternative approach regarding the formation and treatment of osteoporosis from the point of view of the acid-base balance. Therefore, withdrawal of the §103 rejection based on WO '829 is requested.

Mark-up version showing the insertions and deletions of amended claim 1:

1. (Twice Amended) An oral [A] pharmaceutical formulation comprising at least one bisphosphonate and one or more of an additive agent, said additive agent being present in an amount sufficient to provide an enhanced absorption of the bisphosphonate, and said additive being selected from the group consisting of

- a surfactant;
- an ampholytic surfactant;
- an anionic surfactant;
- a cationic surfactant;
- a bile salt;
- a soap and a fatty acid, and a salt thereof;
- a lipid with the exception of a medium chain glyceride or a mixture of medium chain glycerides [having the formula



wherein R^1, R^2 and R^3 are the same or different and each represent a hydrogen atom or an alkanoyl chain having 6 to 18 carbon atoms, wherein at least one of R^1, R^2 and R^3 is an alkanoyl group];

- an oil;
- an enamine;
- a chelating agent;
- a phenothiazine;
- a fatty acid derivative of carnitine or a peptide;
- a substance selected from the group consisting of azone, concanavalin A, a phosphate and a phosphonate derivative;
- a product of a Maillard reaction;
- a polymer;
- a chitosan and a chitosan derivative; and
- combinations thereof.

CONCLUSION

Applicants submit that the claims amendment and remarks are fully responsive to the Office Action. Pending claims 1-21, 23-34, 40-42 and 45-47 are in condition for allowance, which action is earnestly solicited. The Assistant Commissioner is hereby authorized to charge Deposit Account No. 23-1703 in the event that any fee is required in connection with this communication..

Dated: September 17, 2002

Respectfully submitted,

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